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Hematopoietic Stem Cell Transplantation in Multiple Myeloma in the Era of Novel Therapies

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Abstract

Multiple myeloma is the second commonest hematologic malignancy. It is characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow producing a monoclonal immunoglobulin and ultimately causing various complications and organ dysfunction. Over the last 10 years, management of multiple myeloma has dramatically changed due to the introduction of several novel therapies that have improved the disease outcome and prognosis, as well as the quality of life of patients with myeloma due to their safety, tolerability and efficacy. Additionally, the widespread utilization of autologous hematopoietic stem cell transplantation, which is still the standard of care for transplant-eligible patients, and the implementation of new therapeutic strategies such as drug combinations in addition to consolidation and maintenance therapies have resulted in further improvements in response rates and survival in patients with multiple myeloma. This book chapter will be an update on the novel therapies and the recent treatment strategies in myeloma. The role of stem cell treatments in the era of novel therapies will be discussed thoroughly.

Keywords: multiple myeloma, hematopoietic stem cell transplantation, novel therapies, monoclonal antibodies

1. Introduction

Multiple myeloma (MM) is an incurable, debilitating and heterogeneous malignancy that has highly variable clinical course [1–6]. It is a plasma cell neoplasm characterized by neoplastic proliferation of a single clone of plasma cells in the bone marrow (BM) producing a monoclonal immunoglobulin and causing anemia, renal failure, bone destruction and infectious complications [7–9]. It is the second most commonly diagnosed hematologic malignancy (HM)

and it accounts for approximately 10% of all HMs [8]. The median age of MM at diagnosis is 70 years in the United States of America (USA) and 72 years in Europe [9].

2. Diagnosis, staging, genetics and risk stratification

The diagnostic criteria for MM are: (1) clonal BM plasma cells $\geq 10\%$ or biopsy-proven bony or extramedullary plasmacytoma and (2) at least one of the following: (a) evidence of end-organ damage such as anemia, lytic bone lesions, hypercalcemia and renal insufficiency, (b) clonal BM plasma cells $\geq 60\%$, (c) involved:uninvolved serum free light chain ratio ≥ 100 and (d) at least two focal lesions on magnetic resonance imaging [8, 10–15].

MM is usually classified into three stages: (1) stage I; all the following: serum albumin ≥ 3.5 g/dL, serum beta 2 microglobulin (B2M) < 3.5 mg/L, normal serum lactic dehydrogenase (LDH) and no high-risk (HR) cytogenetics; (2) stage II: not fitting stages I and III with serum B2M: 3.5–5.5 mg/L, and (3) stage III; all the following: serum B2M > 3.5 mg/L and HR cytogenetics or elevated serum LDH level [8, 13].

The following cytogenetic abnormalities have been reported in patients with MM: trisomies; monosomies; 17 p deletion; amp (1q20); t(14,16); t(14,20); t(4,14); t(6,14) and t(11,14) [8, 13, 16]. Also, the following molecular mutations have been reported in MM patients: NRAS, KRAS, TP53, BRAF, CCND1, FAM46C, MYC, XBP1, EZH2 and CHST15 [17–21]. Recently, the following laboratory techniques have been utilized in the diagnosis and follow-up of patients with MM: (1) next-generation sequencing (NGS), (2) genomic and epigenetic studies, (3) micro-RNA and (4) minimal residual disease (MRD) evaluation by flow cytometry, polymerase chain reaction, and NGS [17–22]. Mass accumulation rate will be used in the near future for susceptibility of human MM cell lines to standard-of-care therapies [23].

The HR features in MM include: (1) cytogenetic and molecular abnormalities that include: hypodiploid, 17 p deletion, t(4,14), t(14,16), t(14,20) and EZH2; (2) international scoring system stage II or III; (3) presence of comorbid medical conditions that limit therapy; (4) extramedullary disease (EMD) and (5) renal failure, high serum LDH level and plasma cell leukemia [13, 16, 21, 24, 25]. MM patients are stratified into three risk groups based on their cytogenetic profiles as follows: (1) HR that includes 17 p deletion, t(14,16) or t(14,20); (2) intermediate risk that includes: t(4,14) and amp (1q20)/gain (1q) and (3) standard risk that includes: trisomies, t(11,14) and t(6,14) [8, 13, 16]. Additional poor prognostic features include: age ≥ 60 years and refractory and/or relapsed MM (R/R-MM) [26].

3. New insights into the pathogenesis of MM

Despite the recent progress in understanding MM, the pathogenesis of the disease is incompletely understood and is apparently multifactorial in nature [27]. The 10 hallmarks of cancer are: (1) self-sufficiency in growth signaling, (2) evasion of apoptosis, (3) insensitivity to anti-growth mechanisms, (4) tissue invasion and metastases, (5) limitless replicative potential, (6) sustained angiogenesis, (7) avoidance of immune destruction, (8) reprogramming of energy metabolism, (9) tumor-promoting inflammation and (10) genome instability and mutation.

All the 10 hallmarks of cancer are present and active in MM and they contribute to tumor initiation, drug resistance, disease progression and relapse [28–30].

BM adipose tissue is a newly recognized contributor to MM oncogenesis and disease progression, particularly affecting MM cell metabolism, immune action and inflammation in addition to influencing angiogenesis [28]. BM adipose tissue may support MM through: (1) bioactive lipids such as fuel source, signaling molecule and substrate for lipid peroxidation and (2) MM supportive adipokines such as interleukin (IL)-6, tumor necrosis factor- α , MCP-1, PAI-1, resistin and leptin. The interaction between hypoxia, BM adipose tissue and angiogenesis is complicated [28].

The BM niche in patients with MM appears to play an important role in differentiation, migration, survival and drug resistance of malignant plasma cells [31, 32]. The BM niche is composed of (1) cellular compartment that contains the following constituents: hematopoietic and nonhematopoietic cells, stromal cells, osteoblasts, osteoclasts, endothelial cells and immune cells and (2) noncellular compartment, which has the following constituents: extracellular matrix (ECM) and liquid milieu that has cytokines, chemokines and growth factors [31–34]. MM cells home to the BM, adhere to the ECM and BM stromal cells. Trafficking or homing ingress allows progression or metastasis of disease to new BM sites [31].

Bone destruction is the hallmark of MM and is mediated by osteoblasts [35]. Osteoblasts are the most important components of the MM microenvironment. They largely affect disease progression either directly or indirectly. Also, they may slow MM growth [36]. Normally, there is a balance between osteoblastic and osteoclastic activity and imbalance leads to development of disease lesions. Hence, increased osteoclastic activity is associated with MM [37]. Osteoclasts are the primary mediators of bone resorption in both healthy and pathological bone turnover. Bone anabolic agents hold potential for antimyeloma and antiosteolysis therapies [36].

MM pathophysiology is the result of the interaction between clonal plasma cells and the surrounding BM microenvironment [31, 32, 38–40]. BM angiogenesis represents a constant hallmark of MM progression partly driven by the release of proangiogenic cytokines from the tumor plasma cells, BM stromal cells and osteoclasts such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and metalloproteinases [31]. Also, BM stromal cells from MM patients express several proangiogenic molecules such as VEGF, bFGF, angiopoietin-1, transforming growth factor- β , hepatocyte growth factor, platelet-derived growth factor and IL-1 [31]. The signaling pathways that are active in MM microenvironment include Ras GAP, FAK, phosphoinositide 3-kinase (PI-3K)-akt, MEK-ERK and STAT [38]. Other signaling pathways that may also become new therapeutic targets in MM include RANKL, DKK1, sclerostin and activating-A [31, 39].

MicroRNAs play a crucial role in cancer progression [40]. They are the novel crossroads between MM cells and MM microenvironment [41]. Several microRNAs are dysregulated in MM [40]. Dysregulation of microRNAs in MM cells and MM microenvironment has important impacts on initiation of MM, disease progression and drug resistance [42, 43]. Approximately 95 microRNAs are expressed at high levels in MM, particularly miR-125b, miR-133a, miR-1 and miR-124a [40]. Deregulated microRNAs target genes regulating cell cycle, apoptosis, survival and cell growth [40]. Interactions between various constituents of BM microenvironment, particularly MM mesenchymal stem cells and MM cancer stem cells,

may be involved in disease initiation such as bone involvement, disease progression, relapse and drug resistance, so microRNAs may become very useful in designing targeted therapies in the field of precision medicine [27, 44–52]. Additionally, circulating microRNAs may serve as diagnostic and prognostic markers due to their impact on gene expression, biological function and survival, and microRNA-based assays may help in improving risk stratification in MM [27, 53–58].

4. Management of MM

Over the past two decades, management of MM has dramatically changed and this has translated into significant improvements in disease outcomes and prognosis. This unprecedented progress can be attributed to (1) the application of high-dose (HD) chemotherapy followed by autologous hematopoietic stem cell transplantation (HSCT), (2) improvement in supportive care strategies and (3) the introduction of several novel agents particularly immunomodulatory agents and proteasome inhibitors in the treatment of patients with MM [10, 13, 16, 59–61].

Cytotoxic agents that have been used in the treatment of MM include (1) corticosteroids such as dexamethasone and prednisolone, (2) conventional chemotherapies including melphalan, cyclophosphamide, liposomal doxorubicin, bendamustine, carmustine (BCNU), D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) and DCEP (dexamethasone, cyclophosphamide, etoposide, cisplatin) [62]. However, remarkable improvements in survival of patients with MM have been achieved following the introduction of thalidomide, bortezomib and lenalidomide, as well as the recent introduction and approval of the following novel therapeutic agents: (1) newer proteasome inhibitors such as carfilzomib and ixazomib; (2) histone deacetylase inhibitors such as panobinostat and vorinostat; (3) new immunomodulatory drugs such as pomalidomide; (4) monoclonal antibodies such as daratumumab and elotuzumab; (5) Bruton tyrosine kinase inhibitors such as ibrutinib; (6) IL-6 inhibitors such as siltuximab; (7) PI-3 K inhibitors and (8) various immunotherapeutic strategies including chimeric antigen receptor (CAR) T cells [10, 13, 15, 62–64].

5. Frontline and induction therapies in MM

Several studies have shown that VRD (bortezomib, lenalidomide, dexamethasone) regimen is well tolerated and highly effective in the treatment of newly diagnosed MM patients [65–70]. Once used as first-line therapy for MM, VRD has been shown to be superior to the doublet regimen of lenalidomide plus dexamethasone, as well as the triplet regimens VCD (bortezomib, cyclophosphamide, dexamethasone) and VTD (bortezomib, thalidomide, dexamethasone) [68]. Carfilzomib, lenalidomide, dexamethasone (KRD) is an alternative promising regimen but has only been evaluated in small phase II studies in the frontline setting [68].

Response criteria in patients with MM subjected to various therapeutic regimens include MRD evaluation by multicolor flow cytometry or sequencing on bone marrow samples and imaging for EMD [59, 71]. MRD has recently been incorporated into the International

Myeloma Working Group response criteria and new studies have demonstrated that achievement of MRD negativity is a stronger predictor of survival than is traditional complete response (CR) [72].

6. HSCT in patients with MM

6.1. Autologous HSCT

Autologous HSCT, performed at the time of initial diagnosis or at relapse, is considered the standard of care for patients with newly diagnosed MM who are younger than 70 years [8, 73, 74]. Even in the era of novel therapies, timing of performance of autologous HSCT, whether upfront or at relapse, is still controversial although there is global consensus strongly in favor of early autologous HSCT [75].

Autologous HSCT is not curative for MM [8, 73]. Allogeneic HSCT is the only curative therapy for MM but at the expense of increased treatment-related mortality (TRM), so candidates for allografts should be carefully selected from the pool of young patients with R/R-MM [76]. Several randomized clinical trials have shown that, compared with conventional chemotherapy alone, HD chemotherapy followed by stem cell rescue is associated with prolonged event-free survival (EFS) and overall survival (OS) [8, 73, 74]. The recent widespread implementation of autologous HSCT in conjunction with novel therapies has revolutionized the management of MM and has markedly altered the natural history of the disease by improving disease responses and response duration ultimately leading to significant improvement in OS [73].

Eligibility for autologous HSCT is determined by age, performance status, presence and severity of comorbid medical conditions, and frailty score as frailty has been shown to be a predictor of short survival and is considered an exclusion criterion for autologous HSCT [8].

6.2. Cryopreservation versus noncryopreservation of stem cells

For most types of transplants, cryopreservation of HSCs is necessary and is an essential component of the clinical protocol [77]. Dimethyl sulfoxide (DMSO) is widely used as a cryopreservant for various types of stem cells and other body tissues. It has the following adverse effects: skin irritation, garlic breath or body odor; abdominal pain, nausea, vomiting and diarrhea; bronchospasm, chest tightness and dyspnea; altered heart rate and blood pressure, arrhythmias, heart block and myocardial ischemia; various degrees of organ dysfunction and death [77, 78]. Additionally, DMSO has in vitro toxicity in the form of induction of red blood cell hemolysis and reduction in platelet aggregation and activity [78].

Several studies and one meta-analysis have shown that noncryopreserved autologous HSCT for MM is simple, safe and cost-effective and gives results that are at least equivalent to autologous HSCT with cryopreservation [79–84]. TRM at day 100 post-HSCT has ranged between 0.0 and 3.4% [80, 82–84]. Noncryopreserved stem cells can be infused till day 5 postapheresis without viability loss provided they are stored at +4°C in conventional blood bank refrigerator [79, 81, 82, 84]. In a systematic review that included 16 studies having 560 patients with

various HMs including MM, hematopoietic engraftment was universal and only one graft failure was reported [79, 81]. The median times for engraftment following noncryopreserved autografts were 9–14 days for neutrophils and 14–25 days for platelets [79, 81]. Other recent studies on noncryopreserved autologous HSCT in patients with MM have shown the following results: neutrophil engraftment between 10 and 14 days and platelet engraftment between 13 and 25 days postautologous HSCT [85–92].

Melphalan is the standard chemotherapeutic agent that is used in the conditioning therapy prior to autologous HSCT in MM. The dose ranges between 140 and 200 mg/m², given intravenously (IV) [79, 81, 82, 93]. It is cleared from plasma and urine in 1 and 6 hours, respectively. Stem cells can be safely infused as early as 8–24 hours following melphalan administration [79, 81].

Recently, other drugs have been used in the conditioning therapy prior to autologous HSCT in MM either alone or in combination with HD melphalan [94–97]. Compared to HD melphalan, the use of ixazomib, BCNU, bortezomib and IV busulfan either alone or in various combinations with HD melphalan in the conditioning therapies has increased the overall response rates and the median OS without additional toxicity [93–97].

HSCT without cryopreservation has several advantages including (1) simplicity of implementation, (2) allowing autologous HSCT to be performed entirely as outpatient, (3) reduction of transplantation costs, (4) reducing the time between the last induction therapy and HD chemotherapy, (5) prevention of DMSO toxicity, (6) no significant loss of viability of the collected HSCs provided stem cell infusion is made within 5 days of apheresis, (7) expansion of the number of medical institutions performing stem cell therapies and (8) potent engraftment syndrome and autologous graft versus host disease (GVHD) [79–84, 98, 99]. HSCT without cryopreservation has the following disadvantages: (1) plenty of coordination is needed between various teams regarding timing of stem cell mobilization, apheresis, administration of conditioning therapy and infusion of stem cells; (2) limitation of the use of standard HD chemotherapy schedules such as BEAM (BCNU, etoposide, cytarabine and melphalan) employed in the autologous HSCT for lymphoma and (3) inability to store part of the collection and reserving it for a second autologous HSCT in case a rich product is obtained [79–84].

6.3. Outpatient HSCT

MM is the leading indication for autologous HSCT worldwide. Patients with MM are ideal candidates for outpatient autologous HSCT because of the following reasons: the ease of administering HD melphalan, the relatively low extra-hematological toxicity and the short period of neutropenia [85].

Outpatient autologous HSCT for MM is not yet established as a routine procedure, due to reluctance of certain centers and due to the absence of guidelines. However, reduction of costs and period of hospitalization are the driving forces behind the adoption of outpatient HSCT. The mixed inpatient/outpatient model has been shown to be highly feasible with very low rates of rehospitalization and TRM [100, 101].

Several studies have shown safety, feasibility and cost-effectiveness of outpatient autologous HSCT for MM [86–90]. Selection criteria for outpatient autologous HSCT include expected compliance, proximity to the HSCT center for daily visits, 24-hour caregiver support, favorable

performance status and favorable comorbidity profile [91]. Lack of caregiver is a limiting factor for outpatient autologous HSCT [92].

6.4. Tandem and second AHSCT

Even before the era of novel therapies, tandem autologous HSCT had been performed in patients with MM and the results of tandem transplants showed superior outcomes compared to single autologous HSCTs [102, 103]. Later on, two single-center retrospective analyses showed higher rates of progression-free survival (PFS) and OS in patients subjected to tandem autologous HSCT compared to recipients of single autologous HSCT [104, 105]. A meta-analysis that included six studies comparing tandem to single autologous HSCT in patients with MM showed: (1) no difference between the two forms of autologous HSCT with respect to OS and EFS and (2) tandem autologous HSCT was associated with improved response rates but at the expense of increased TRM [106]. However, this meta-analysis was criticized as it included a study with significant statistical errors [107].

Several studies have shown that a second autologous HSCT used as part of salvage therapy in patients with MM relapsing after the first autologous HSCT has been found to be safe and feasible particularly in carefully selected patients [108–112]. Factors associated with the success of second autologous HSCT include younger age, B2M < 2.5 mg/L at diagnosis, remission duration > 9 months from first autologous HSCT, > partial response achieved in response to the first autologous HSCT and performance of second autologous HSCT before relapse and within 6–12 months from the first autologous HSCT [113, 114].

6.5. Allogeneic HSCT in MM

Although allogeneic HSCT represents the only potentially curative therapeutic modality in patients with MM, it is associated with relatively high TRM [76, 115, 116]. The advent of reduced intensity conditioning (RIC) and the application of autologous-allogeneic tandem HSCT approaches have broadened the use of allogeneic HSCT in patients with MM. Autologous-allogeneic tandem HSCT may overcome the negative impact of 17 p deletion and/or t(4,14) and the achievement of molecular remission in patients having HR cytogenetics has resulted in long-term freedom from disease [117].

In patients with HR disease or those relapsing after autologous HSCT, particularly younger patients who are fit for allografts, salvage therapy with novel agents followed by RIC allogeneic HSCT has been shown to provide significant PFS benefit [76, 118–121]. In patients lacking human leukocyte antigen (HLA)-matching sibling donors, alternate donors such as matched unrelated donors, cord blood transplantation and haploidentical forms of allogeneic HSCT have been employed and they have shown feasibility and effectiveness [115, 122–124].

7. Consolidation and maintenance therapies in MM

Almost all patients with MM relapse after autologous HSCT. Hence, treatment given in the postautologous HSCT period is aimed at suppression of residual disease in order to prolong duration of response, OS and PFS while minimizing toxicity [125, 126].

The use of novel therapies in the consolidation phase following single or tandem autologous HSCT has been shown to enhance the rate as well as the quality of response thus contributing to improvements in clinical outcomes including prolongation of PFS [126]. Bortezomib-based regimens used as consolidation therapy after autologous HSCT in patients with MM have been shown to be effective in the improving PFS and decreasing relapse rate [127].

Maintenance therapy represents an important therapeutic strategy to delay disease progression and relapse [125, 126]. The following drugs have been used in postautologous HSCT maintenance: interferon, thalidomide, bortezomib and carfilzomib [125, 126, 128–130]. Bortezomib is safe, well tolerated and efficacious and it can be used with no risk of second malignancy till disease progression, but its disadvantages include cost and effects on quality of life (QoL) [126, 130].

In February 2017, the Food and Drug Administration in the USA approved the use of lenalidomide as maintenance therapy after autologous HSCT for patients with MM, after showing efficacy and safety in several studies [131]. Lenalidomide has tumoricidal and immunomodulatory activities against MM [132]. Several studies have shown the efficacy of lenalidomide maintenance after autologous HSCT as this therapy has been shown to be associated with significant improvements in OS, PFS and longer time to disease progression [133–136]. A multicenter, randomized double-blind study that included 306 patients with newly diagnosed MM ≥ 65 years of age and ineligible for autologous HSCT treated initially with melphalan, prednisolone and lenalidomide induction followed by lenalidomide versus placebo maintenance showed the following results: (1) significant prolongation of PFS, (2) maximum benefit was achieved in patients 65–75 years of age and (3) 3-year second primary tumor of 7% in the lenalidomide arm versus 3% in the placebo arm [132]. Other studies on lenalidomide maintenance have shown more toxicity and low rate of development of second tumors [133, 134]. Lenalidomide maintenance can be initiated as early as day 100 postautologous HSCT [133]. Duration of lenalidomide maintenance longer than 3 years has been associated with further improvement in survival [134]. Several studies performed in patients with newly diagnosed MM subjected to autologous HSCT have shown continuous therapy to be more effective in prolongation of OS and PFS that limited the duration of treatment [137–141].

8. Novel therapies in MM

The novel therapies that have recently been introduced into the treatment of MM include (1) proteasome inhibitors such as bortezomib, carfilzomib and ixazomib; (2) immunomodulatory agents such as thalidomide, lenalidomide and pomalidomide; (3) monoclonal antibodies such as daratumumab and elotuzumab and (4) histone deacetylase inhibitors such as panobinostat, in addition to other classes of medications that can also be used in the treatment of MM such as glucocorticoids, DNA alkylating agents, as well as doxorubicin, cisplatin and etoposide [10, 13, 15, 62–64]. Novel agents and targeted therapies that are either currently used or under development for the treatment of MM are shown in **Table 1** [61, 62, 142–150].

Several cell cycle regulatory proteins have been proposed as therapeutic targets in patients with MM. Other targets that have already been identified in MM include microtubules,

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1. **Monoclonal antibodies:** Anti-CD 38 (daratumumab, elotuzumab, isatuximab, MOR202), anti-CD138 (indatuximab ravtansine), anti-interleukin-6 (siltuximab), anti-RANKL (denosumab), anti-KIR2DL1/2/4 (IPH2101)
 2. **Immunomodulatory agents:** thalidomide, lenalidomide, pomalidomide
 3. **Proteasome inhibitors:** bortezomib, carfilzomib, ixazomib
 4. **Histone deacetylase inhibitors:** panobinostat, vorinostat, romidepsin, ricolinostat
 5. **mTOR inhibitors:** everolimus, temsirolimus
 6. **Checkpoint (programmed cell death protein 1) inhibitors:** nivolumab, pembrolizumab
 7. **Bruton’s tyrosine kinase inhibitors:** ibrutinib
 8. **BCL2 antagonists (BH3 mimetics):** venetoclax, obatoclax, navitoclax
 9. **Cyclin-dependent kinase inhibitors:** dinaciclib
 10. **MEK inhibitors:** selumetinib
 11. **Kinesin spindle protein 1 inhibitors:** filanesib, array 520
 12. **Selective inhibitors of nuclear transport:** selinexor
 13. **Phosphoinositide 3-kinase-Akt inhibitors:** perifosine, afuresertib
 14. **PIM kinase inhibitors:** LGH 447
 15. **Vaccines:** PVH-410
 16. **Chimeric antigen receptor T cells (CAR T cells):** directed against:
 - a. CD-19
 - b. CD-38
 - c. B-cell maturation antigen
 - d. Cell surface glycoprotein
-

Table 1. Novel agents and targeted therapies that are either currently used or under development for the treatment of multiple myeloma.

kinesin motor proteins, aurora kinases, polo-like kinases and the anaphase-promoting complex/cyclosome [151]. The novel therapies that are used in the treatment of MM differ in their modes of action. Nevertheless, each drug has its own side effects that should be considered particularly once treating patients with comorbid medical conditions and once these novel agents are used in combination with other drugs [152].

8.1. Daratumumab

Daratumumab is a human IgG_k monoclonal antibody that targets CD38, which is a cell surface protein that is overexpressed in MM cells. It is given IV at a dose of 16 mg/kg weekly [153–156]. It induces death of MM cells by several mechanisms including (1) complement-dependent cytotoxicity, (2) antibody-dependent cell-mediated cytotoxicity, (3) antibody-dependent cellular phagocytosis and (4) apoptosis [153–156].

Daratumumab has shown substantial efficacy as monotherapy in heavily pretreated patients with MM as well as in combination with bortezomib in patients with newly diagnosed MM [154]. Two phase III randomized clinical trials in R/R MM using daratumumab in combination with either bortezomib and dexamethasone or lenalidomide and dexamethasone showed

significantly longer PFS with manageable toxicity [154, 156]. In a phase III randomized clinical trial performed in patients with newly diagnosed MM, not eligible for autologous HSCT, the addition of daratumumab to bortezomib, melphalan and prednisolone decreased the risk of death and disease progression but was also associated with higher rates of infections [155]. The adverse effects of daratumumab include infusion-related reactions, hematologic toxicity in the form of neutropenia and thrombocytopenia and various infectious complications [153–156].

8.2. Elotuzumab

Elotuzumab is an immunostimulatory monoclonal antibody targeting signaling lymphocyte activation molecule F7 (SLAMF7) [157]. While no responses to elotuzumab as a single agent were obtained, the addition of elotuzumab to lenalidomide and dexamethasone in RR-MM patients resulted in overall response rate (ORR) of 79% compared to 66% ORR obtained with lenalidomide and dexamethasone alone [142, 158]. Also, in a phase III randomized clinical trial in patients with R/R-MM, the combination of elotuzumab, lenalidomide and dexamethasone decreased the risks of death and disease progression by 30% [157].

8.3. Pomalidomide

Pomalidomide is a third-generation immunomodulatory agent that has been approved for patients with progressive MM or those who have received at least two lines of therapy [159]. It has been shown to be effective in combination with dexamethasone \pm carfilzomib or other agents in patients with R/R-MM or in those with HR cytogenetics [159–162]. The use of pomalidomide combined with low-dose dexamethasone in heavily pretreated patients with R/R-MM has been shown to be cost-effective as the combination has produced clinical outcomes comparable to those obtained by daratumumab alone or carfilzomib alone [5].

8.4. Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor [163]. It is well tolerated and causes minimal neurotoxicity. It has demonstrated promising activity in patients with MM who are refractory to bortezomib or immunomodulatory agents [163–165]. It can be combined with dexamethasone or other novel agents [164–166].

It is able to sensitize 24% of bortezomib-refractory MM patients. When combined with dexamethasone in R/R-MM, it resulted in superior outcome in terms of ORR and PFS compared to bortezomib and dexamethasone combination [158]. Also, it is under evaluation for patients with newly diagnosed MM [166].

8.5. Panobinostat

Histone deacetylase inhibitors such as panobinostat and vorinostat have demonstrated some activity against MM and they have multiple proposed mechanisms of actions once used in the treatment of MM [167]. Panobinostat is a potent oral pan-deacetylase inhibitor. It affects growth and survival of MM cells through alteration of (1) gene expression through epigenetic modification and (2) protein metabolism by inhibiting protein degradation [168–171]. The approval of panobinostat for the treatment of MM was based on the results of phase III randomized double-blind clinical trial (PANORAMA 1), which demonstrated improvement in

median PFS of 7.8 months for panobinostat, bortezomib and dexamethasone in comparison with placebo, bortezomib and dexamethasone [168–171]. Panobinostat, in combination with bortezomib and dexamethasone, was recently approved in the USA, Europe and Japan for the treatment of patients with MM who had failed at least two prior regimens including bortezomib and an immunomodulatory agent [168–171]. A meta-analysis that included 11 clinical trials and 700 patients with R/R-MM treated with panobinostat demonstrated not only efficacy but also safety of panobinostat in combination with other agents [172]. The main toxic effects of panobinostat are thrombocytopenia and diarrhea. However, several studies showed other adverse effects including lymphopenia, neutropenia and anemia, nausea, vomiting, constipation and abdominal pain, asthenia, fatigue, peripheral edema and peripheral neuropathy [167–172]. Ongoing clinical trials are evaluating the role of panobinostat in combination with drugs other than bortezomib in R/R-MM, in combination with various drugs in newly diagnosed disease and in maintenance therapy of myeloma [169].

8.6. CAR T cells

CAR is a hybrid antigen receptor that is composed of an extracellular antigen-binding domain and an intracellular signaling domain. T cells genetically targeted with a CAR to B-cell malignancies have demonstrated tremendous clinical outcome [173]. Immunotherapy using CAR-mediated T cells has demonstrated high response rates in patients with B-cell malignancies. CAR T-cell therapy is a cellular therapy that redirects a patient's T cells to specifically target and destroy tumor cells [174]. CARs are genetically engineered fusion proteins composed of antigen recognition domain derived from a monoclonal antibody as well as an intracellular T-cell signaling domain and a costimulatory domain [174].

There are multiple steps in the production of CAR T cells and these include (1) leukapheresis to separate leukocytes; (2) enrichment of leukapheresis product with T cells; (3) separation of T-cell subsets at the level of CD4/CD8 composition using specific antibody-based conjugates or markers; (4) T-cell selection or activation, gene transfer or genetic modification and viral transduction; (5) volume expansion of T cells, isolation, washing and culture followed by cryopreservation and (6) infusion of CAR T cells [174, 175].

Adverse effects of CAR T-cell therapy include cytokine release syndrome (CRS), neurotoxicity, on target/off tumor recognition and anaphylaxis. Additionally, theoretical toxicities of CAR T cells include clonal expansion secondary to insertional oncogenesis, GVHD and off-target antigen recognition [176]. Management of CAR T-cell toxicity includes supportive measures, immunosuppression with tocilizumab (IL-6) receptor blockade for CRS and suicide or elimination genes to allow for selective depletion of CAR T cells [176].

CAR expressing T cells have demonstrated success in the treatment of B-cell lymphoid malignancies particularly CD19+ acute lymphoblastic leukemia and chronic lymphocytic leukemia [177]. Cell surface glycoprotein (CS1) is highly expressed on MM cells and is an ideal target for the treatment of MM, that is, CS1 can be targeted by CAR natural killer cells to treat MM [177]. A patient with advanced and refractory MM received myeloablative treatment with melphalan 140 mg/m², followed by autologous HSCT, and then infusion of CTL019 CAR resulted in CR with no disease progression for 12 months after CAR T-cell infusion [178]. CAR T cells can target the following antigens in patients with MM: B-cell maturation antigen (BCMA), CD138, CD19 and kappa-light chain [179]. A bispecific T-cell engager (BiTE)

targeting BCMA and CD3_E (BI 836909) has been developed and it has been shown to be highly potent and efficacious to selectively deplete BCMA-positive MM cells; thus, it represents a novel immunotherapeutic approach in the treatment of MM [180]. CARs are proteins that incorporate antigen domain, costimulatory domains and T-cell activation domains [181]. Only a limited number of patients with MM received CAR T-cell therapy, but preliminary results are encouraging [179].

BCMA is only expressed on some B cells, normal plasma cells and malignant plasma cells. The first clinical trial using CAR T cells targeting BCMA that is expressed in most cases of MM included 12 patients [181]. After dose escalation in the infusion of CAR-BCMA cells was used, the trial showed remarkable success and impressive activity against MM cells as BM plasma cells became undetectable by flow cytometry and patients entered stringent CR lasting for 17 weeks before relapse [181]. Another clinical trial using CAR-BCMA that included 21 patients showed increase in response rate from 89 to 100% after dose escalation [182].

9. Refractory and/or relapsed MM (R/R-MM)

The course of MM progression is highly variable as almost all patients with MM who respond to initial therapy will eventually relapse and require further treatment [6]. The introduction of novel agents over the last 15 years, the implementation of new therapeutic strategies and the adoption of drug combinations that include highly effective and tolerable drugs have improved (1) the clinical outcome dramatically as response rates have increased from approximately 30% with single agents to about 90% with combination therapies and (2) the QoL even in heavily pretreated patients. However, determining the optimal sequence and combination as well as timing of each agent is necessary [6]. In a retrospective analysis of 628 patients with newly diagnosed MM who developed relapse after initial therapy, it was found that prolonged duration of treatment was associated with improved survival [141]. Unfortunately, secondary plasma cell leukemia and EMD still present difficult therapeutic challenges [16].

There is no standard of care for MM relapse after autologous HSCT [183, 184]. Regimens that are composed of combination therapy with (1) drugs having synergistic effect and no cross-resistance and (2) one or two novel therapies are generally preferred as they lead to deeper and longer responses that are translated into improved survival [16, 183–185]. However, treatment should be individualized based on toxicity as well as patient and disease characteristics [184]. A meta-analysis of phase III randomized controlled trials showed that, compared to doublet regimens, triplets resulted in improved OS, PFS, very good partial response and CR although the risk of having grade III/IV drug adverse effects was higher with triplet regimens [185].

Mechanisms of drug resistance in MM include (1) multidrug-resistant gene polymorphism, (2) P-glycoprotein overexpression in MM cells, (3) microenvironmental changes, (4) clonal evolution including, (5) cancer stem cells, (6) upregulation and downregulation of various micro-RNAs and (7) selected CD34+, CD 138+, B7-, H1+, CD19- plasma cell accumulation after treatment [40].

Therapeutic options for patients with R/R-MM include (1) salvage therapy; combination of old and new therapies such as (a) bortezomib, thalidomide, cisplatin, cyclophosphamide, etoposide and doxorubicin (VTD-PACE); (b) KRD/carfilzomib, pomalidomide and dexamethasone

(KPD) ± PACE or (c) daratumumab-based therapy; (2) second autologous HSCT; (3) allogeneic HSCT in carefully selected patients and (4) enrollment in clinical trials [8, 11, 13, 16]. Specific agents that are used in the treatment of R/R-MM include (1) immunomodulatory agents such as thalidomide, lenalidomide and pomalidomide; (2) proteasome inhibitors such as bortezomib, carfilzomib and ixazomib; (3) monoclonal antibodies such as daratumumab and elotuzumab; (4) histone deacetylase inhibitors such as panobinostat and (5) pembrolizumab [6, 142, 157, 158, 164, 186]. The use of pembrolizumab (antiprogrammed cell death 1) in combination with lenalidomide and dexamethasone in patients with R/R-MM resulted in 76% ORR [142, 158].

10. Management of MM patients having renal failure

Renal impairment (RI) is one of the most common complications of MM as 20–50% of patients with newly diagnosed MM present with RI, while 40–50% of patients develop RI during the course of the disease and about 5% of myeloma patients have dialysis-dependent renal failure (RF) at presentation [187–191]. In patients with MM, the causes of RI include myeloma cast nephropathy, excess of monoclonal free light chains causing proximal renal tubular damage, dehydration, infectious complications, hypercalcemia, hyperuricemia, use of nephrotoxic drugs and contrast media, hyperviscosity, myeloma cell infiltration and amyloid deposition [187–189, 192].

Bortezomib, thalidomide, lenalidomide and dexamethasone in various combinations can be used in the treatment of MM patients having RF and their use has been associated with high response rates and recovery of even partial or complete recovery of renal function [187–189, 191, 192]. In early chemotherapy trials, RF was considered a predictor of poor prognosis, patients with hemodialysis were reported to have a poorer prognosis and RF was considered an exclusion criterion from autologous HSCT because of the concerns about higher rates of treatment-related toxicity and nonrelapse mortality (NRM) due to mucositis, infectious complications and encephalopathy [187, 190]. However, recent studies have shown that autologous HSCT in patients with MM and RF has been associated with partial or complete recovery of renal function even in dialysis-dependent patients [190]. Therefore, autologous HSCT can be offered to patients with MM and RF with acceptable toxicity and NRM and a significant improvement in renal function that may be encountered in approximately one third of patients [187, 190]. In patients with MM and RF, a melphalan dose of 200 mg/m² can be administered in the conditioning therapy of auto-HSCT without an increase in toxicity and NRM [190].

Kidney transplantation is the treatment of choice for most patients with end-stage renal failure (ESRD) as it is associated with improved survival and QoL compared to hemodialysis [193]. Even in patients with MM having RF, kidney transplantation is a valid therapeutic option in well-selected patients who achieve control of their disease and maintain a durable remission preferably for 3–5 years and have stable light chain levels but this option should be considered early in the course of the disease [194–197]. Combined HSCT, predominantly autologous HSCT, and renal transplantation have been performed for patients having various hematological disorders such as plasma cell dyscrasias [198–202]. Patients with MM having ESRD, either on regular hemodialysis or not, can be offered not only HSCT but also combined HSCT and renal transplantation either simultaneously or sequentially [198, 199, 203–206].

11. Conclusions and future directions

The introduction of several novel agents and targeted therapies over the last 10 years has revolutionized the management of MM and has produced unprecedented outcomes in terms of disease control and OS. Currently, novel agents and targeted therapies are used in the following settings: (1) prior to HSCT to reduce tumor burden and to optimally control MM, (2) following HSCT as consolidation and maintenance therapy to allow long-term disease control and (3) as salvage therapy in case of relapse of MM after HSCT.

However, novel agents and targeted therapies should not be considered as a form of replacement to HSCT, but instead these two valuable therapeutic interventions should be considered complementary to each other. The smart combination of novel agents and targeted therapies with various forms of HSCT in the new treatment paradigm of MM will ultimately lead to higher cure rates and longer disease controls.

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